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REVIEW

Treatment Options in Cushing's Disease

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Abstract: Endogenous Cushing's syndrome is a grave disease that requires a multidisciplinary and individualized treatment approach for each patient. Approximately 80% of all patients harbour a corticotroph pituitary adenoma (Cushing's disease) with excessive secretion of adrenocorticotropin-hormone (ACTH) and, consecutively, cortisol. The goals of treatment include normalization of hormone excess, long-term disease control and the reversal of comorbidities caused by the underlying pathology. The treatment of choice is neurosurgical tumour removal of the pituitary adenoma. Second-line treatments include medical therapy, bilateral adrenalectomy and radiation therapy. Drug treatment modalities target at the hypothalamic/pituitary level, the adrenal gland and at the glucocorticoid receptor level and are commonly used in patients in whom surgery has failed. Bilateral adrenalectomy is the second-line treatment for persistent hypercortisolism that offers immediate control of hypercortisolism. However, this treatment option requires a careful individualized evaluation, since it has the disadvantage of permanent hypoadrenalism which requires lifelong glucocorticoid and mineralocorticoid replacement therapy and bears the risk of developing Nelson's syndrome. Although there are some very promising medical therapy options it clearly remains a second-line treatment option. However, there are numerous circumstances where medical management of CD is indicated. Medical therapy is frequently used in cases with severe hypercortisolism before surgery in order to control the metabolic effects and help reduce the anestesiological risk. Additionally, it can help to bridge the time gap until radiotherapy takes effect. The aim of this review is to analyze and present current treatment options in Cushing's disease.

Keywords: Cushing's disease, operative treatment, medical therapy, bilateral adrenalectomy, radiotherapy

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Introduction

Endogenous Cushing's syndrome is a grave and devastating condition. Eighty percent of the patients harbour an adrenocorticotropin-hormone (ACTH) secreting pituitary adenoma (Cushing's disease), while extrapituitary tumour (ectopic ACTH syndrome) and ectopic CRH-secreting tumours are very rare findings. The remaining 20% of ACTH-independent Cushing's syndrome are (in most instances) due to an adrenal tumour or, more rarely, macronodular adrenal hyperplasia, primary pigmented nodular disease (either as isolated disease or as part of the Carney complex), or the McCune-Albright syndrome.[1,2]

In Cushing's disease (CD), the elevated ACTH secretion leads to an excess of adrenal gland cortisol secretion. The autonomous ACTH-secretion by the adenoma and the disturbance of the normal cortisol feedback mechanism with the hypothalamo-pituitary-adrenal (HPA) axis leads to a loss of the circadian rhythm of cortisol production, excessive cortisol production and hypercortisolism. The clinical consequences for the patients are grave and include high blood pressure, diabetes, loss of libido, menstrual disorders, weight gain, hirsutism, acne, easy bruising, purplish skin striae, osteoporosis, muscle weakness, depression and cognitive impairment.[1,3,4] Although externally visible clinical signs of the pathology are often strikingly obvious, the rare incidence and low prevalence[5] of the disease leads to a considerable delay between the onset of symptoms and the establishment of diagnosis.[6,7] One has to consider that patients often present with obesity, arterial hypertension, diabetes mellitus, and depression in the early stage of their disease which are wide spread diseases. This can hinder the early detection of CD and complicate the diagnosis. On the other hand, untreated CD is accompanied by a significantly higher mortality compared to the general population due to vascular and metabolic comorbidities so that early disease detection is of paramount importance.[1,5,8–13]

The goals of treatment in CD are the normalization of cortisol excess, long-term disease control, avoidance of recurrence and reversal of clinical features.[14] The initial therapy of first choice is transsphenoidal surgery (TS) for tumour removal. Survival rates of patients cured by TS do not differ from those in the general population.[15,16] In the event of failure after initial or repeat pituitary surgery, second-line treatment options include medical therapy, radiotherapy or bilateral adrenalectomy.

To date, the treatment of this complex pathology remains a challenge. Only a close interdisciplinary treatment concept involving neurosurgeons, endocrinologists, oncologists and radiotherapists can guarantee a curative treatment result with lasting disease control for the patients. In this review, focus is laid on current treatment options in Cushing's disease and old and new medical treatment options for CD are analyzed.

Surgical Treatment of CD

Transsphenoidal microsurgical removal of ACTH-secreting pituitary adenoma is the first-line treatment in CD.[14] Although endoscopic surgery has gained increasing recognition as an alternative to the classical microscopic technique,[17] robust data about outcome with this treatment modality are still scarce; a recent review of endoscopic surgery showed an overall remission rate of 74% in CD,[18] while the reported overall success rates of transsphenoidal microsurgery for CD vary from 68.5% to 94%.[19–23] Despite an ongoing competitive discussion whether microscopy or endoscopy is the superior technique for transsphenoidal surgery, one has to keep in mind that the most important determinant of surgical outcome is the experience of the neurosurgeon, since both, endoscope and microscope, are only visualising devices.

Remission rates, prognostic factors for successful surgical treatment and the role of preoperative imaging results

A significant correlation between remission rates, tumour size (with higher remission rates in microadenomas) and the degree of invasive growth pattern (ie, invasion of the basal dura and/or the cavernous sinus) has been shown.[19,23–26] In microadenomas, a positive MRI finding with a clear visualization of the adenoma is associated with remission rates between 72.3% to 100% of the cases,[23,25,27] while remission rates in cases with negative or inconclusive MRI drop to only 64.7%–71.4%.[25,28,29] In cases where MRI is negative, inferior petrosal sinus sampling (IPSS) offers a further diagnostic tool.[19,30] However, IPSS is only able to predict the correct laterality of a microadenoma in 60%–70% of the cases,[20,27,31,32] so that it has been abandoned by some specialized centres in cases where pituitary-dependence of CD has been clearly verified

during endocrinological evaluation.[23] Further important prognostic factors for successful surgery include (i) histological confirmation of ACTH-secreting tumour, (ii) low post-operative serum-cortisol levels and (iii) long-lasting adrenal insufficiency after surgery.[14,15,24,33] In cases with negative MRI where no adenoma is readily detected during surgery, different strategies have been applied ranging from stepwise exploration of the pituitary body[21] to total hypophysectomy.[25]

Recent publications by Ikeda et al showed very promising results in detecting early-stage Cushing adenomas by the use of composite methionine-positron emission tomography (MET-PET) and 3.0-tesla MRI. The authors investigated a series of 35 patients with CD and compared the detection rate of adenomas by the use of superconductive MRI (1.5 or 3.0 tesla) and composite images from FDG-PET. They found a 100% detection rate (verified by surgical pituitary exploration) when using composite MET-PET/3.0-T MRI, while the detection rate of FDG-PET/3.0-T MR imaging was 73%. Superconductive MRI only detected microadenomas in 40% correctly.[34]

Recurrence rates and success rates of re-operation

The overall recurrence rate is 5%–10% at 5 years and 10%–20% at 10 years. Recurrence occurs more likely and earlier in patients with macroadenomas compared to those with microadenomas (mean of 16 vs. 49 months).[26,33] In recurrent CD, repeat transsphenoidal surgery has been shown to be effective in 46% to 71% of patients.[28,35–40] Because of significant scar tissue and altered normal anatomy, repeat surgery for recurrent pituitary adenomas is in general more challenging than an initial operation or an immediate re-operation for persistent disease. Ikeda et al (2011) found that the use of MET-PET was extremely helpful in the detection of adenoma in recurrent CD in one 45 year old female patient.[41] Surgical navigation and the Doppler probe are highly recommended for localizing the portion of the internal carotid artery (ICA) within the cavernous sinus and for confirming regional anatomy.[39,42]

Complications of surgery

The most common surgical complications of transsphenoidal surgery include diabetes insipidus, cerebrospinal fluid (CSF) leakage, vascular complications (occlusion and bleeding), and hypopituitarism. The reported rate of permanent diabetes insipidus ranges from 1% to 6%,[15,16,20,27,43] while the rate of hypopituitarism (other than the desired adrenal insufficiency) lies between 8.7% to 53% in different series.[15,16,20,25,27,43] Hypopituitarism is clearly correlated with the extent of surgery, more radical procedures yielding higher complication rates[14,15,24] and a higher rate of post-operative hypopituitarism.[15,25] Also, repeat surgery is associated with a higher rate of CSF leakage and hypopituitarism.[44,45]

Radiotherapy

In cases with persistent or recurrent disease where operative treatment options have been exhausted (eg, due to tumour invasion of the cavernous sinus), radiotherapy is a well-established second-line therapy. Radiotherapy is either performed as fractionated external beam radiotherapy or stereotactic surgery (SR). Fractionated radiotherapy is indicated for adenomas with proximity to the optic pathways and with large volume. SR is used for small adenoma volumes. Circumscribed residual adenomas within the cavernous sinus are particularly suitable for SR. For fractionated radiotherapy, the remission rates in the literature are heterogeneous and range from 10% to 83%. In larger series of SR, remission rates are about 50%.[46–49] Typical radiation doses in conventional radiotherapy range from 45 to 54 Gray (Gy).[50] SR is usually performed as a single fraction dose. Margin doses reported in the literature usually range from 15–32 Gy.[51]

The main disadvantage of both radiotherapeutic procedures is the delayed response to treatment. For both procedures the mean reported time to remission interval is 3 years after treatment,[47,48,52–55] and effective anti-secretory drugs should be used until the response becomes evident. Hypopituitarism is the most frequent side effect of radiotherapy in ACTH-secreting adenomas and occurs in over 50% of the cases after fractionated radiotherapy[47,54,56,57] and up to 66% after SR.[50] Additionally, radiotherapy may cause damage to the brain and the cranial nerves, especially the optic apparatus.[46] The risk for second tumour formation is considered to be in the range of 1%–2% with conventional radiotherapy.[54] Studies providing longer follow up data after SR are still necessary. However, reports about the development of cranial nerve deficits and deterioration of visual acuity to complete loss after a

second treatment with SR clearly suggest caution for the repetitive use of SR.[48,58] After an initial response to both types of radiotherapy, relapse may still occur, so that long-term follow up is necessary.[50,59]

Bilateral Adrenalectomy

Bilateral adrenalectomy is the second-line treatment for persistent hypercortisolism that offers immediate control of hypercortisolism. The morbidity of the operative procedure itself can be minimized by the use of endoscopic approaches. However, this treatment option requires a careful individualized evaluation and is generally only indicated in (i) patients with persistence of hypercortisolism despite medical therapy, (ii) intolerance to medical therapy, (iii) as an alternative to long-term medical treatment after failed pituitary radiotherapy or (iv) younger women who wish to maintain fertility.[12,14]

This treatment option clearly has the disadvantage of permanent hypoadrenalism that necessitates a lifelong glucocorticoid and mineralocorticoid replacement therapy.[60] Additionally, it bears the risk of developing Nelson's syndrome, so that a close endocrinological follow-up with ACTH evaluation and regular MRI scans are mandatory in all adrenalectomized patients.[60,61]

Medical Therapy

Although there are some very promising prospects due to the development of new drugs that have recently given medical treatment in CD significant space, it clearly remains a second-line treatment option. However, there are numerous circumstances where medical management of CD is indicated. Medical therapy is frequently used in cases with severe hypercortisolism before surgery in order to control the metabolic effects and help reduce the anestesiological risk.[62] Moreover, medical treatment plays a pivotal role in patients waiting for the full effect of pituitary radiotherapy and is often essential for patients where surgery has failed to control CD, since it helps reducing or normalizing hypercortisolemia. It has been claimed that medical therapy should always be performed before considering bilateral adrenalectomy.[12] However, early bilateral adrenalectomy should be considered after surgical failure in patients who are threatened by severe comorbidities because of uncertain control of Cushing's disease with medical treatment and delayed control by RT.

Furthermore, in the rare cases of CD patients with metastatic disease (although far more common in cortisol secreting adrenal cancer), medical therapy is a helpful palliative treatment modality.[14]

Medical therapeutic agents for treatment of CD can be divided into two categories: adrenal enzyme inhibitors and neuromodulatory agents.

Adrenal Enzyme Inhibitors

Ketoconazole

Usually, ketoconazole is widely used in the medical treatment of CD. Ketoconazole is an imidazole derivative and was initially developed as an oral antifungal drug. It inhibits sex-steroid synthesis by its action on C17–20 lyase[61] and cortisol synthesis by preventing cholesterol side chain cleavage (inhibiting 17α-hydroxylase and 18α-hydroxylase activity).[64,65] Treatment usually starts with a dose of 200 mg twice daily and may be increased until 1200 mg daily given in four doses.[66–68] The adjustment of doses is based on the 24-hour urine free cortisol (UFC) levels.[62]

Efficacy

In a metaanalysis of eight trials with daily ketoconazole doses ranging from 400 to 1200 mg, an average normalization of UFC levels was found in up to 93% of patients who took their medication consequently without interruption.[69]

Side effects

The most common side effect is hepatic dysfunction with elevated levels of serum transaminases.[69] Hepatotoxicity is dose-dependent and reversible when the drug is discontinued. Other side effects include nausea, vomiting, skin rash, and loss of libido and potence in males due to decreased sex-steroid synthesis. This drug is contraindicated in pregnant females due to teratogenicity.[12] Ketoconazole is a potent cytochrome P450 enzyme inhibitor, and has interactions with the following drugs: benzodiazepines aside from lorazepam; a variety of calcium channel blockers such as nifedipine and verapamil; 3-hydroxy-3-methyl-glutaryl- CoA reductase inhibitors, aside from pravastatin and fluvastatin; phenytoin; warfarin; and theophylline. Histamine-2-receptor blockers and proton pump inhibitors should be avoided during treatment with ketoconazole as its absorption depends on gastric acidity.[60] Ketoconazole

is usually used in combination with other adrenal enzyme inhibiting drugs in order to minimize side effects of high drug doses. The second reason is that high doses of ketoconazole lead to increased ACTH levels that overwhelm the drug's inhibitory effects.[62]

Metyrapone

Metyrapone is another drug that can be used as an adjunctive treatment for Cushing disease.[70] It blocks the production of cortisol by inhibiting 11β-hydroxylase production of cortisol from deoxycortisol in the adrenal gland. The resultant relative decrease of cortisol may stimulate further ACTH secretion as an aftermath, increasing adrenal androgen and aldosterone precursors with weak mineralocorticoid activity. Metyrapone is usually started in a dose of 250 mg three times daily and can be titrated up to a maximum of 6 g per day.

Efficacy

Metyrapone has shown efficacy over an extended period of treatment.[62,71] In a large series of 53 CD patients, short-term mean serum cortisol levels of ≤400 nmoL/L were obtained in 75% of patients and effective long-term effects were observed in 83% of the 24 patients who received the drug after pituitary irradiation (mean 2250 mg/day, median 27 months).[72] In severe cases of CD, a block-and-replace scheme can be used for immediate reversal of hypercortisolism.

Side effects

The mean side effects are hirsutism, acne, gastrointestinal upset and dizziness. Hypertension, edema or hypokalemia due to raised mineralocorticoid effects are rare, but may require the discontinuation of therapy.[63]

Aminoglutethimide

Aminoglutethimide prevents conversion of cholesterol to pregnenolone, thus inhibiting not only cortisol but also estrogen and aldosterone production. The usual dose given is 250 mg twice or thrice daily.

Efficacy

Aminoglutethimide seems to be less efficient in CD compared to other causes of CS[67,69] and is most often used as an adjunct to metyrapone for reducing doses and the drug toxicity.

Side effects

The primary side effect is a generalized, self-limited pruritic rash that is usually manageable with antihistamines without requiring drug cessation. Other side effects include dizziness, blurred vision, and, as the drug blocks thyroid hormone synthesis, hypothyroidism. Cholestasis and bone marrow suppression are very rare side effects. Aminoglutethimide is a cytochrome P450 enzyme inducer and may have several potential interactions with other medications, including the decrease of ketoconazole levels. Additionally, it increases the metabolism of dexamethasone but not of hydrocortisone, so that the latter is often used in patients requiring steroid replacement therapy.[73,74]

Mitotane

Mitotane inhibits several steps in glucocorticoid synthesis through inhibition of 11α-hydroxylase, 18-hydroxylase, 3α-hydroxylase, hydroxysteroid dehydrogenase and several cholesterol side chain cleavage enzymes.[73,74] Today, its primary use is in patients with adrenocortical carcinoma, since doses greater than 4 g per day have an adrenolytic action in adrenal cortical cell mitochondria and lead to carcinoma cell destruction and cellular necrosis.[62,77] Mitotane is often started at 250 to 500 mg nightly with slow escalation of the dose to 4 to 12 g/day.

Efficacy

In a large historical study with 46 CD patients receiving 4 to 12 g of Mitotane per day, a remission rate of 83% was observed within 8 months after initiation of treatment.[78] Sixteen patients received a combination of mitotane and radiotherapy and disease control was achieved in all of them. Another study with a lower-dose mitotane regime (up to 4 g/day) in order to reduce side effects showed remission in 29 of 36 patients (81%) with adjunctive radiotherapy.[79] In 17 of these patients, no long-term mitotane therapy was necessary, pointing to a persistent adrenolytic effect after the drug is stopped. Monitoring of morning serum cortisol is performed after starting mitotane treatment, and once a decline is observed, prednisone or dexamethasone replacement therapy can begin as needed. Usually, the use of prednisone is more favorable since its metabolism is not increased by mitotane.[80]

Side effects

The severe side effects of mitotane limit its use in CD and have essentially set it as second or third line medication after ketoconazole.[62] The most commonly documented drug-related side effects are nausea and hypercholesterolemia.[78] At higher doses, neurological side effects are common, including gait ataxia, vertigo, confusion, and word finding difficulties.[76] Patients receiving mitotane therapy without radiotherapy are at risk to develop Nelson syndrome. Finally, the drug is teratogenic and therefore contraindicated in pregnant women.[81]

Etomidate

Etomidate, a commonly used short-acting intravenous anesthestic, is an exceedingly potent inhibitor of 11β-hydroxylase as well as an inhibitor of 17α-hydroxylase.[63] It is mainly reserved for acute control of hypercortisolemia due to its sedative effects and sole availability in intravenous form.[62] Although in one study in which the authors used it at a dose of 0.3 mg/kg/hour with a normalization of serum cortisol levels within 12 hours in six patients with CD, its use in daily practice remains limited.[82]

Neuromodulatory Agents

To date, the search for more "specific" drugs that may act on ACTH secretion at the pituitary adenoma level without interfering with other hormone synthesis and with less severe side effects that may allow for primary treatment is still ongoing. Some promising agents involve somatostatin analogs and dopamine agonists which already play an important role in the treatment of acromegaly[83] and prolactinomas.[12] Although the results in CD are still mainly experimental with few clinical results, it is worth while to dedicate a section of this review to neuromodulatory active agents.

Somatostatin (SS) analogs

Preclinical studies in cultured rat pituitary corticotrophs show expression of multiple somatostation receptors (SST), including subtype 2 (sst_2) and subtype 5 (sst_5).[84]

Two studies[85,86] investigated the effects of SS analogs in human corticotroph adenoma tissues: a superior ACTH inhibition by pasireotide as compared to octreotide[85] and a dissociation between the anti-secretory and anti-proliferative effects of pasireotide were observed.[86]

In clinical studies the use of the currently available somatostatin analogs octreotide and lanreotide were, other than in acromegaly,[83] mostly ineffective in CD. However, more promising results have been reported with the new somatostatin analogue pasireotide.[3] Pasireotide has a high affinity to sst_5 which predominates in corticotroph adenomas.[14] A recently published phase II, proof-of-concept, open-label, single arm, multicenter study of pasireotide enrolled 39 CD patients from 10 centers.[3] Study participants self-administered pasireotide 600 μg twice a day for 15 days at 0900 and 2100 h. Ten patients did not respond to the treatment, 76% of the participants showed a decrease of urinary free cortisol (UFC) levels, but only five of them (17%) had normalized UFC levels after 15 days. The mean UFC levels in the overall cohort decreased from baseline by 44.5%. Additionally, a trend toward a lower baseline UFC level as predictive factor for a response to pasireotide ($P = 0.102$) was observed, while no significant differences between ACTH values between responders and non-responders were observed. The most observed side effects of the medication were gastrointestinal disorders (54%), diarrhea (44%), abdominal pain (18%), nausea (23%) and hyperglycemia (36%).

Dopamine agonists

In humans, no conclusive data exist as to whether or not dopamine agonist receptors (DA) have an immediate regulatory effect on ACTH release in normal corticotroph cells.[87] In this context, the intermediate lobe (despite being a rudimentary structure) seems to play a significant role, since it maintains important biological functions: corticotroph adenomas arising from there are more likely to respond to DA treatment with the classical substance bromocriptin.[88] The results of a 24-month treatment with cabergoline in 20 CD patients was recently presented: a maintained control of cortisol excess was found in 40% and an induced tumor shrinkage in 20% of patients, treatment doses varying between 1 and 7 mg cabergoline/week.[89] While the authors did not report any significant side effects of the therapy in their study population (with the exception of 2 patients who developed hypotension associated with severe asthenia that forced them to discontinue the medication),

it is noteworthy that the drug has been reported to be responsible for an increased prevalence of cardiac valve insufficiency[12] in patients with long-term cabergoline therapy.

Combined treatment with SS analogs and DA agonists

Since both, SST and DA receptors are present in human corticotroph adenomas, a combination therapy of both substances appears to be a further reasonable treatment approach that is currently object to clinical trials. A very recent study enrolling 17 CD patients achieved a sustained normalization of UFC levels in 5 patients (29%) with a pasireotide monotherapy. The addition of cabergoline led to a normalization of UFC in further 4 patients (24%). At day 60 of treatment, 9 patients (53%) had normalized UFC levels, while all but one of the remaining 8 patients with persistently high UFC levels showed a tendency toward normalization (mean decrease of the UFC level 48% ± 6%).[90]

Glucocorticoid receptor antagonist

Mifepristone (known as RU486) is the latest competitive antagonist to glucocorticoids that was engineered to block the peripheral effects of glucorticoids. Similar to the GH peripheral antagonist pegvisomant that is successfully used in acromegaly[91] its efficacy can be judged by its medical response but not by levels of ACTH or cortisol. Currently, there is no significant clinical experience reported yet with its use in treatment of CD. Side effects are hyperpigmentation, hypertension, hypokalemia, psychosis, and cardiomypathy.[62]

Other Neuromodulatory Agents

These include retinoic acid and peroxisome proliferator-activated receptor-γ PPAR-γ (rosiglitazone). Retinoic acid showed an in vitro antiproliferative action as well as ACTH and corticosterone inhibition. In vivo these effects were confirmed in mice with experimental ACTH secreting tumors as well as in dogs with CD. While the efficacy of retinoic acid in humans still needs to be tested in clinical trials, the clinical trials with rosiglitazone led to disappointing results. One study including 14 CD patients (7 with unsuccessful surgery, 7 yet untreated) showed a significantly lowered 24 hour UFC in 6 patients with a dose varying between 8–16 mg of rosiglitazone for 1–7 months.[92] Another study enrolling 10 patients (4 untreated yet, 4 with relapse after surgery, 2 after failed surgery) did not find any significant reduction of 24 hour UFC after a median treatment of 3 months (range 1–8 months) with a dose of 4–16 mg rosiglitazone.[93] The reported side effects included weight increase, edema, somnolence and hirsutism. While rosiglitazone was used in most studies, the results of one study with pioglitazone showed similar unencouraging results: 5 patients received a treatment of 45 mg for 30 days, with no lowering of 24 hour UFC in any study participant.

Alkylating agents in aggressive ACTH producing adenomas/carcinomas

Temozolomide, an orally administered alkylating agent, has recently demonstrated to have a significant activity against aggressive pituitary tumours resistant to multimodality therapy. These tumours are associated with substantial morbidity and mortality.[94–97] There is strong evidence that low O^6-methylguanine-DNA-methyltransferase (MGMT) immunoexpression correlates with response to temozolomide chemotherapy,[94,97] since MGMT is a DNA repair enzyme that removes alkylating adducts induced by temozolomide and counteracts its effects. A very recent review article evaluating the response rates in 40 reported pituitary tumour cases described an overall response rate of 60%. The best response rates were observed in prolactinomas (73%) as well as in ACTH-secreting tumours (60%), while non-functioning adenomas showed lower response rates (76%).[96]

Conclusions

CD is a very severe condition that requires early detection as well as rapid curative treatment and effective disease control in order to avoid long-term sequelae of the disease. The first treatment of choice is the neurosurgical tumor removal, most cases being operated via a transsphenoidal approach. In cases where the surgical procedure alone cannot achieve disease control, second-line treatment options have to be considered. These consist of medical therapy, radiotherapy and bilateral adrenalectomy. Treatment results with somatostatin-analogues directed to the receptor subtype 5 are promising and might offer an option for long-term medical therapy. SR radiotherapy is increasingly

used for circumscribed residual adenomas within the cavernous sinus. Therefore, the search for new and effective medical tools is still open. All these aspects emphasize the need of effective treatment of CD itself as well as long-term follow-up of these patients in order to control its complications and detect recurrence in a timely fashion.

Disclosures

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